UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, vs. HOECHST MARION ROUSSEL, INC. and TRANSKARYOTIC THERAPIES, INC., Defendants.	Civil Action No. 97-10814-WGY

DEFENDANTS' ANSWER TO AMENDED COMPLAINT

Defendants Transkaryotic Therapies, Inc. ("TKT") and Hoechst Marion Roussel, Inc. ("HMR"), for their answer to the individual paragraphs in the Amended Complaint, state as follows:

1. The defendants deny the allegations of paragraph 1 of the Amended Complaint, except that they admit (a) that this is a civil action in which the plaintiff Amgen, Inc. ("Amgen") purports to invoke the jurisdiction of the court pursuant to 28 U.S.C. § 1338 and 2201-2202 and (b) that venue lies in this District.

2. The defendants admit the allegations of paragraph 2 of the Amended Complaint.

3. The defendants deny the allegations of paragraph 3 of the Amended Complaint, except that they admit that HMR is an indirect subsidiary of Hoescht AG, a German corporation, that HMR itself is a Delaware corporation, and that this Court has personal jurisdiction over HMR for the purpose of this case.

4. The defendants admit the allegations of paragraph 4 of the Amended Complaint.

5. The defendants deny the allegations of paragraph 5 of the Amended Complaint, except (a) that they admit that Amgen was founded in 1980 and that Amgen introduced Epogen in 1989; and (b) that the defendants are without knowledge or information sufficient to admit or deny the allegations of paragraph 5 relating to the number of persons who have been treated with Epogen, the number of persons employed by Amgen or Amgen's practices or policies with respect to the payment of dividends.

6. The defendants deny the allegations of paragraph 6 of the Amended Complaint, except that they admit that erythropoietin is a glycoprotein hormone; that erythropoietin stimulates red blood cell production in the body; and that glycoproteins contain an amino acid backbone associated with carbohydrate residues linked at certain positions on the amino acid backbone.

7. The defendants deny the allegations of paragraph 7 of the Amended Complaint, except that they admit that in human adults erythropoietin is produced and secreted by kidney cells; that erythropoietin is present in blood and urine among other sites; that knowledge of erythropoietin and its biological function has existed for a great many years; and that, prior to 1983, erythropoietin has been isolated and purified, but not completely characterized, by persons unrelated to the parties to this case.

8. The defendants deny the allegations of paragraph 8 of the Amended Complaint, except that they admit that, beginning in the 1970's, proteins were

produced by inserting (transfecting) exogenous DNA sequences encoding those proteins together with regulatory sequences into cells which, subsequent to transfection, were capable of producing the desired proteins; and that in the 1970's, techniques existed for isolating, identifying and transfecting exogenous protein-encoding DNA sequences together with regulatory sequences.

9. The defendants deny the allegations of paragraph 9 of the Amended Complaint, except (a) that the defendants admit that Amgen has produced commercial quantities of Epogen, and that Epogen has been deemed to be a therapeutically useful product; and (b) that the defendants are without sufficient knowledge or information to admit or deny the allegations of paragraph 9 that Amgen began research in the field of erythropoietin prior to August, 1981 or that Amgen's Dr. Lin was the first to isolate successfully the human erythropoietin gene.

10. The defendants deny the allegations of paragraph 10 of the Amended Complaint, except (a) that they admit that, in 1989, Amgen received approval from the United States Food & Drug Administration to market Epogen in the United States for the treatment of anemia associated with kidney failure, that the permitted therapeutic uses of Epogen have since been expanded to include the treatment of anemia resulting from other causes, that in some instances treatment with Epogen is beneficial to patients, and that on information and belief, worldwide sales of erythropoietin products by several companies is over three billion dollars; and (b) that the defendants are without knowledge or information sufficient to admit or deny the allegations of paragraph 10 with respect to the number of kidney dialysis patients who are today receiving treatment for Epogen.

11. The defendants deny the allegations of paragraph 11 of the Amended Complaint, except that they admit that Epogen is a therapeutically useful product; and that Epogen was and is produced in transfected non-human origin cells.

12. The defendants deny the allegations of paragraph 12 of the Amended Complaint, except that they admit that the United States Patent and Trademark Office has granted a number of patents to Amgen; and that the first such patent is believed by defendants to be United States Patent No. 4,703,008. The defendants state that the claims of the '008 patent -- which are not at issue in this case -- speak for themselves. The defendants further admit that, in litigation between Amgen and Genetics Institute, this Court held that Genetics Institute did prove by clear and convincing evidence that certain asserted claims of the '008 patent were invalid, but failed to prove by clear and convincing evidence that other asserted claims were invalid; and that the United States Court of Appeals for the Federal Circuit affirmed aspects of this Court's decision. The defendants further admit that, from time to time, Amgen has filed continuation applications which Amgen claims are based upon the disclosures contained in the application for the '008 patent. The defendants state that the claims contained in these continuation applications speak for themselves.

13. The defendants deny the allegations of paragraph 13 of the Amended Complaint, except that they admit that, in 1989, three interferences were declared in the United States Patent and Trademark Office between certain claims in the '008 patent and certain claims in the pending Amgen patent applications, on the one hand, and claims in pending applications assigned to Genetics Institute, on the other hand, to determine questions of priority among the claims of the respective parties. The

defendants admit that the interferences were decided adversely to Genetics Institute; that Genetics Institute appealed those decisions; and that the appeal was settled. The defendants state that the claims that were at issue, and the decisions rendered in the interferences, speak for themselves.

14. The defendants deny the allegations of paragraph 14 of the Amended Complaint, except that they admit that, on August 20, 1996, the United States Patent and Trademark Office issued U.S. Patent No. 5,547,933, a copy of which is attached to the Amended Complaint as Exhibit A. The defendants state that the '933 patent speaks for itself.

15. The defendants deny the allegations of paragraph 15 of the Amended Complaint, except that they admit that, on April 8, 1997, the United States Patent and Trademark Office issued U.S. Patent No. 5,618,698, a portion of which is attached to the Amended Complaint as Exhibit B. The defendants state that the '698 patent speaks for itself.

16. The defendants deny paragraph 16 of the Amended Complaint, except that they admit that, on April 15, 1997, the United States Patent and Trademark Office issued U.S. Patent No. 5,621,080, a portion of which is attached to the Amended Complaint as Exhibit C. The defendants state that the '080 patent speaks for itself.

17. The defendants deny the allegations of paragraph 17 of the Amended Complaint, except that they admit that, on May 26, 1998, the United States Patent and Trademark Office issued U.S. Patent No. 5,756,349, a portion of which is attached to the Amended Complaint as Exhibit D. The defendants state that the '349 patent speaks for itself.

18. The defendants deny the allegations of paragraph 18 of the Amended Complaint, except that they admit that on September 21, 1999, the United States Patent and Trademark Office issued U.S. Patent No. 5,955,422, a portion of which is attached to the Amended Complaint as Exhibit E. The defendants state that the '422 patent speaks for itself.

19. The defendants are without knowledge or information sufficient to admit or deny the allegations of paragraph 19 of the Amended Complaint, and therefore deny those allegations.

20. The defendants deny the allegations of paragraph 20 of the Amended Complaint, except that they admit that TKT commenced operations in 1988; that it has developed a novel method of producing proteins, including proteins which potentially have therapeutic value; that TKT has developed a cell line for a product that has been called Gene Activated Erythropoietin ("GA-EPO"), that GA-EPO is not produced by isolation from human urine or by isolation from human blood; that GA-EPO is produced in a human cell line containing, among other things, endogenous human DNA encoding human erythropoietin; and that the GA-EPO expressing human cell line is produced by being transfected with certain exogenous DNA sequences (which exogenous sequences do not encode erythropoietin) that are inserted into the human cell line in order to permit GA-EPO to be expressed.

21. The defendants deny the allegations of paragraph 21 of the Amended Complaint, except that they admit that HMR is an indirect subsidiary of Hoechst AG, and that TKT and HMR have entered into certain agreements. The defendants state that these agreements speak for themselves.

22. The defendants deny the allegations of paragraph 22 of the Amended Complaint, except that they state that the TKT/HMR agreements speak for themselves.

23. The defendants deny the allegations of paragraph 23 of the Amended Complaint, except that they admit that TKT has announced that it has successfully developed a GA-EPO cell line sufficient for scale-up commercial production levels and that the cell line has been accepted by HMR; that the defendants submitted an IND to the United States Food and Drug Administration in May, 1997; that there have been public pronouncements, each of which speaks for itself; and that TKT has stated that erythropoietin products are well-known to regulatory authorities in many countries of the world, and that it believes that clinical development of GA-EPO can be accomplished in a focused and timely manner.

24. The defendants deny the allegations of paragraph 24 of the Amended Complaint, except that they admit that they have the technical and financial resources to introduce a gene-activated erythropoietin product into the United States market, if clinical trials proceed as planned, and if and when they receive regulatory approval for the manufacture and sale of such a product.

25. The defendants deny the allegations of paragraph 25 of the Amended Complaint, except that they admit that the process for the manufacture of GA-EPO does not involve isolation from urine; that in preliminary animal testing, they have demonstrated that GA-EPO has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells; that defendants have made and used GA-EPO in this country but, as this Court ruled on April 15, 1998,

in accordance with 35 U.S.C. § 271(e)(1), "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs . . ."; that GA-EPO is produced in a human cell line containing, among other things, endogenous human DNA encoding human erythropoietin; and that the GA-EPO expressing human cell line is produced by being transfected with certain exogenous DNA sequences (which exogenous sequences do not encode erythropoietin) that are inserted into the human cell line in order to permit GA-EPO to be expressed.

26. The defendants deny the allegations of paragraph 26 of the Amended Complaint, except that they admit that the process for the manufacture of GA-EPO does not involve isolation from urine; that in preclinical animal testing, they have demonstrated that GA-EPO has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells; that defendants have made and used GA-EPO in this country but, as the Court ruled on April 15, 1998, in accordance with 35 U.S.C. § 271(e)(1), "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs . . ."; that GA-EPO is produced in a human cell line containing, among other things, endogenous human DNA encoding human erythropoietin; and that the GA-EPO expressing human cell line is produced by being transfected with certain exogenous DNA sequences (which exogenous sequences do not encode erythropoietin) that are inserted into the human cell line in order to permit GA-EPO to be expressed.

27. Defendants deny the allegations of paragraph 27 of the Amended Complaint.

28. Defendants deny the allegations of paragraph 28 of the Amended Complaint.

29. Defendants deny the allegations of paragraph 29 of the Amended Complaint, except that they admit in August 1996, TKT released a Prospectus in connection with a 2.5 million share offering, that in October 1996, TKT issued an Amended Prospectus, and that by letter dated September 4, 1996, Amgen made certain statements to TKT. The defendants state that each of these documents speaks for itself.

30. Defendants deny the allegations of paragraph 30 of the Amended Complaint, except that they admit that they have stated, in substance, that they do not believe that they infringe any valid Amgen patent, but that, in the light of Amgen's conduct, it would not be surprising if Amgen were to initiate a lawsuit against TKT and/or HMR at some point in the future; that defendants moved, on June 9, 1999, to reopen this suit, but only with respect to Amgen's action for a declaratory judgment with respect to future activities.

31. Defendants deny the allegations of paragraph 31 of the Amended Complaint, except that they admit, as stated in their June 9, 1999 motion, that the GA-EPO manufacturing process has been finalized; that they presently plan to market a gene-activated erythropoietin product in the United States, but only after obtaining regulatory approval for the commercial manufacture and sale of such a product, if such approval is ultimately obtained.

32. Defendants deny the allegations of paragraph 32 of the Amended Complaint, except that they admit that TKT stated in 1994 that it did not believe that it required a license from Amgen in order to make, use or sell a gene therapy product (a product which is not relevant to any allegation in the Amended Complaint); that TKT has stated that its technology does not involve the transfection of exogenous DNA encoding erythropoietin; that since August 20, 1996, TKT and HMR have stated their intention to proceed with the development of a gene-activated erythropoietin product, and with the effort to obtain FDA approval for the manufacture and sale of such a product; and that TKT has issued a Prospectus, certain Amended Prospectuses and certain press releases and served and filed a June 9, 1999 motion, each of which speaks for itself. Defendants further admit that TKT raised $37.5 million in its initial public offering and that TKT's stock price increased after the completion of that public offering.

33. Defendants deny the allegations of paragraph 33 of the Amended Complaint, except that they admit that TKT issued a Prospectus, and an Amended Prospectus dated October 11, 1996, each of which speaks for itself, and that HMR has established a manufacturing capability that can produce substantial amounts of GA-EPO in a cost-effective manner.

34. Defendants deny the allegations of paragraph 34 of the Amended Complaint.

35. Defendants deny the allegations of paragraph 35 of the Amended Complaint.

36. Defendants deny the allegations of paragraph 36 of the Amended Complaint, except that they admit that, on June 9, 1999, defendants moved to reopen

only Amgen's action for declaratory judgment with respect to future activities; that Amgen joined in this request; and that on June 10, 1999, the Court granted "the motion to reopen [the] case for declaratory judgment."

37. Defendants deny the allegations of paragraph 37 of the Amended Complaint, except admit that, on April 15, 1998, the Court ordered "the ... declaratory judgment claim administratively closed, to be reopened upon motion of either party for good cause" shown; that TKT and HMR moved on June 9, 1999 to reopen Amgen's action for declaratory judgment with respect to future activities; that Amgen joined in this request; and that on June 10, 1999, the Court granted "the motion to reopen [the] case for declaratory judgment."

DEFENSES

1. The Amended Complaint fails to state a claim upon which relief can be granted. This includes, without limitation, the fact that defendants' actions do not constitute acts of infringement by reason of 35 U.S.C. § 271(e)(1), as the Court ruled on April 15, 1998. Therefore, at a minimum, those paragraphs of the Complaint which refer to allegations of infringement (e.g., ¶ 25 ["has . . . constitute[d] infringement"], ¶ 26 ["has . . . infringe[d]"], ¶ 30 ["infringes" and "has infringed"], ¶ 31 ["infringement"] and ¶ 1 ["has infringed"] of the prayer for relief) do not state a claim upon which relief can be granted.

2. No claim of United States Patent No. 5,547,933 is infringed by any product made, used, or sold, or any process used, by TKT or HMR; and each claim of the '933 Patent, if construed to cover any such TKT or HMR product or process, is invalid insofar as it is construed to cover that product or process.

3. United States Patent No. 5,547,933 is invalid for failure to comply with the legal standards statutorily mandated by 35 U.S.C. § 101 et seq., including but not limited to 35 U.S.C. §§ 101, 102, 103 and 112.

4. No claim of United States Patent No. 5,618,698 is infringed by any product made, used, or sold, or any process used, by TKT or HMR; and each claim of the '698 Patent, if construed to cover any such TKT or HMR product or process, is invalid insofar as it is construed to cover that product or process.

5. United States Patent No. 5,618,698 is invalid for failure to comply with the legal standards statutorily mandated by 35 U.S.C. § 101 et seq., including but not limited to 35 U.S.C. §§ 103 and 112.

6. No claim of United States Patent No. 5,621,080 is infringed by any product made, used, or sold, or any process used, TKT or HMR; and each claim of the '080 Patent, if construed to cover any such TKT or HMR product or process, is invalid insofar as it is construed to cover that product or process.

7. United States Patent No. 5,621,080, and each and every claim thereof, is invalid for failure to comply with the legal standards statutorily mandated by 35 U.S.C. § 101 et seq., including but not limited to 35 U.S.C. §§ 101, 102, 103 and 112.

8. No claim of United States Patent No. 5,756,349 is infringed by any product made, used, or sold, or any process used, TKT or HMR; and each claim of the '080 Patent, if construed to cover any such TKT or HMR product or process, is invalid insofar as it is construed to cover that product or process.

9. United States Patent No. 5,756,349 is invalid for failure to comply with the legal standards statutorily mandated by 35 U.S.C. § 101 et seq., including but not limited to 35 U.S.C. §§ 101, 102, 103 and 112.

10. No claim of United States Patent No. 5,955,422 is infringed by any product made, used, or sold, or any process used, TKT or HMR; and each claim of the '080 Patent, if construed to cover any such TKT or HMR product or process, is invalid insofar as it is construed to cover that product or process.

11. United States Patent No. 5,955,422 is invalid for failure to comply with the legal standards statutorily mandated by 35 U.S.C. § 101 et seq., including but not limited to 35 U.S.C. §§ 101, 102, 103 and 112.

12. United States Patent Nos. 5,547,933; 5,618,698; 5,621,080; 5,756,349 and 5,955,422 ("the patents-in-suit") are unenforceable due to acts, misrepresentations and omissions of material fact made by the applicant or by his agents or assigns constituting inequitable conduct in connection with the proceedings in the United States Patent and Trademark Office which resulted in the grant of the patents-in-suit, made, on information and belief, with the intent to deceive the United States Patent and Trademark Office, including without limitation the failure to cite material and relevant art; providing incomplete and misleading information in the specification of the applications for the patents-in-suit; and the failure to correct information in the specification of the applications for the patents-in-suit which applicant or his agents or assigns knew, should have known or learned was incorrect.

WHEREFORE, the defendants request that this Court dismiss this action with prejudice, that it deny all relief to Amgen, that it declare this to be an exceptional

case within the meaning of 35 U.S.C. § 285 and award to the defendants the costs of this action including a reasonable attorneys' fee, and that it grant to the defendants such other and further relief as it deems just in the circumstances.

Respectfully submitted,

October 22, 1999

TRANSKARYOTIC THERAPIES, INC.,
and HOECHST MARION ROUSSEL, INC.

By their attorneys,

CHOATE, HALL & STEWART
Robert S. Frank, Jr. (BBO #177240)
Eric J. Marandett (BBO #561730)
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000

FISH & NEAVE
Herbert F. Schwartz
Kenneth B. Herman
James F. Haley, Jr. (BBO #217220)
1251 Avenue of the Americas
New York, NY 10020
(212) 596-9000

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CERTIFICATE OF SERVICE
I hereby certify that a true copy of the above document was served upon the attorney of record for each other party by [redacted] (by hand) on 10/22/99